


Attorney Docket No.: T4903.CIP (UT-0003)  
Inventors: Rao and Majtaba  
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 neuroepithelial stem cells, thereby generating said neural crest stem cells.[.]

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Please cancel claim 14.

#### REMARKS

Claims 1-14 are pending in the instant application. Claims 1-14 have been rejected. Claim 1 has been amended. Claim 14 has been canceled. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

#### I. Rejection of Claims 1-14 under 35 U.S.C. § 112

Claims 1-14 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

With respect to claim 1, the Examiner suggests that it is unclear how the neuroepithelial cells are induced to differentiate into neural crest stem cells as there is no induction step recited in the method. With respect to claim 2, the Examiner suggests that the phrase "said inducing further comprises replating" lacks antecedent basis. With respect to claims 3, 5 and 8, the Examiner

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suggests that it is unclear what the first induction step encompasses and how the chick embryo can be withdrawn when there is no recitation of a mitogen in either claim 1 or 2. With respect to claim 6, the Examiner suggests that the phrase "wherein said inducing step comprises withdrawing a mitogen" is vague and indefinite because it is unclear how a mitogen can be withdrawn when there is no recitation of a mitogen in claim 1.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 1 to set forth steps of induction and to provide clarity and antecedent basis with respect to replating and withdrawal of mitogens as set forth in claims dependent therefrom. Support for the amendments to claim 1 can be found throughout the specification and in particular at page 9, lines 5-18, page 10-11, lines 19-2, and in the Examples at pages 19-20, 46-49, and 51-53.

With respect to claim 9, the Examiner suggests that it is unclear what amount of dorsalizing agent is required for induction. Applicants respectfully traverse this rejection. MPEP § 2173 is quite clear; definiteness of claim language must be analyzed, not in a vacuum, but in light of:

- (A) The content of the particular application disclosure;
- (B) The teachings of the prior art; and

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(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Clearly, specific amounts of dorsalizing agents to be added for induction should not be required in the claim when one of skill in the art could ascertain such amounts routinely based upon prior art teachings relating to dorsalizing agents such as those cited by the Examiner in this Office Action and the teachings in the specification.

Finally, with respect to claim 14, the Examiner suggests that the claim is incomplete as there is no induction steps recited in the claim. It is respectfully point out, however, that Applicants have canceled claim 14, thus mooted this rejection.

Withdrawal of these rejections is respectfully requested in light of the amendments to the claims and the above remarks.

## II. Rejection of Claims 1-3, 5, 6, 8 and 14 under 35 U.S.C. § 102(a)

Claims 1-3, 5, 6, 8 and 14 have been rejected under 35 U.S.C. § 102(a) as being anticipated by Rao et al. (Society for Neuroscience Abstracts, Vol. 22, Part 1, page 527, Abstract #215.12, 1996). The Examiner suggests that Rao et al. teach a method of generating neural crest stem cells comprising culturing

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neuroepithelial cells in the presence of FGF and chick embryo extract (CEE), and inducing neuroepithelial stem cells to differentiate in vitro, thereby generating said neural crest stem cells.

Accordingly, in an earnest effort to advance the prosecution, Applicants have provided a Declaration herewith which clearly establishes that the Abstract by Rao et al. is not the work of another. This Declaration makes clear that the co-authors, Kalyani and Hobson, while contributing to the technical details and experiments reported in this Abstract, did not contribute to the actual invention.

Accordingly, the Abstract by Rao et al. is not a valid reference under 35 U.S.C. §102(a). It is therefore respectfully requested that this rejection be withdrawn.

### **III. Rejection of Claims 1, 2 and 14 under 35 U.S.C. § 102(b)**

Claims 1, 2 and 14 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Ray et al. (J. Neuroscience 14:3548-3564, 1994). The Examiner suggests that Ray et al. teach a method for generating mammalian neural crest cells comprising inducing neuroepithelial stem cells to differentiate *in vitro*, thereby

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generating neural crest stem cells. Applicants respectfully disagree.

Contrary to the Examiner's suggestion, the method of Ray et al. relates to neuroblasts which are defined as embryonic spinal cord cells which have already committed to a neuronal pathway and are expressing a neuronal phenotype. See specifically the Abstract and page 3549, column 2 wherein neuroblasts are defined. In contrast, in the method of the present invention, neural crest stem cells are induced from an isolated, pure, homogeneous population of mammalian neuroepithelial stem cells.

In an earnest effort to advance the prosecution of this case and to clarify distinctions between of the method of the present invention and the teachings by Ray et al., Applicants have amended claim 1 to specify that the mammalian neural crest stem cells are produced by first isolating a pure, homogeneous population of neural epithelial stem cells. Support for this amendment can be found throughout the specification and in particular at page 9, lines 5-18, page 10-11, lines 19-2, and in the Examples at pages 19-20, 46-49, and 51-53. MPEP § 2131 requires that a reference teach every element of a claim to be anticipating. Since Ray et al. does not teach a method for isolating a population of neural

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epithelial stem cells, this reference cannot anticipate the claims as amended.

Withdrawal of this rejection under 35 U.S.C. § 102(b) is therefore respectfully requested.

#### IV. Rejection of Claims 1, 6-8 and 14 under 35 U.S.C. § 102(e)

Claims 1, 6-8 and 14, have been rejected under 35 U.S.C. § 102(e) as being anticipated by Anderson et al. (U.S. Patent 5,589,376). Claims 1, 6-8 and 14 have also been rejected under 35 U.S.C. § 102(e) as being anticipated by Anderson et al. (U.S. Patent 5,824,489). The Examiner suggests that these references teach methods of generating mammalian neural crest stem cells comprising inducing neuroepithelial stem cells to differentiate in vitro, thereby generating the neural crest stem cells. Applicants respectfully traverse this rejection.

As acknowledged by the Examiner, the methods of Anderson comprise culturing neural tubes onto fibronectin-coated plated and isolating the neural crest cells. However as discussed in Section III, *supra*, claims of the instant application have been amended to specify that the neural crest stem cells are induced from an isolated pure, homogeneous population of neuroepithelial stem cells. Since neither of the cited Anderson references teach this

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element, they cannot anticipate the claimed invention as amended.  
See MPEP § 2131.

Accordingly, withdrawal of these rejections is respectfully requested.

**V. Rejection of Claims under 35 U.S.C. § 103(a)**

Claims 4, 7 and 9-13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Rao et al. (Society for Neuroscience Abstracts Vol. 22, Part 1, page 527, Abstract #215.12, 1996), taken with Varley et al. (Experimental Neurology, 140:84-94, 1996). Applicants respectfully traverse this rejection.

As discussed in Section II, *supra*, the primary reference by Rao et al. is not a valid prior art reference for purposes of 35 U.S.C. § 102 or § 103 and the secondary reference by Varley et al. is insufficient alone to render the instant claimed invention obvious.

Varley et al. teach a method for obtaining neural crest cells from explantation of quail embryos and culturing the neural crest cells in the presence of BMP-2 or BMP-4. In contrast, the instant claims have been amended and are now drawn to a method for generating mammalian neural crest stem cells from a pure, homogeneous population of mammalian neuroepithelial stem cells

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derived from the neural tube from a mammalian embryo at a stage of embryonic development after closure of the neural tube. The teachings of Varley et al. alone clearly fail to provide the requisite reasonable expectation of success nor the teaching or suggestion of all the claim limitations to render the instant claimed invention obvious.

Withdrawal of this rejection under 35 U.S.C. § 103 is therefore respectfully requested.

Claims 9-13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Ray et al. (J. Neuroscience 14:3548-3564, 1994) taken with Varley et al. (Experimental Neurology 140:84-94, 1996). Claims 9-13 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over Anderson et al. (U.S. Patent 5,589,376) or alternatively, over Anderson et al. (U.S. Patent 5,824,489). Applicants respectfully traverse these rejections.

As discussed in Sections III and IV, *supra*, the claims of the instant application have been amended and are now drawn to a method of generating neural crest stem cells from an isolated, pure, homogeneous population of neuroepithelial stem cells. None of the cited prior art references teach these cells nor a method for obtaining these cells. Accordingly, these references fail to provide the requisite expectation of success nor the teaching or



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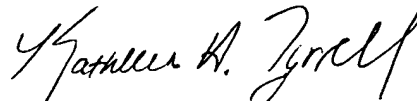
suggestion of all claim limitations to render the instant invention, as now claimed, obvious.

Withdrawal of these rejections is therefore respectfully requested.

#### VI. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



Kathleen A. Tyrrell  
Registration No. 38,350

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LICATA & TYRRELL P.C.  
66 E. Main Street  
Marlton, New Jersey 08053

(856) 810-1515